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LETTER TO THE EDITOR

RET mutations and medullary thyroid cancer

I read with interest the report in the *Journal of the Formosan Medical Association* by Chang et al[1] on *RET* mutations in patients with medullary thyroid cancer (MTC). The authors observed 15 patients with MTC, and noted that all eight patients with a family history, or with other phenotypes of multiple endocrine neoplasia type 2 (MEN 2), had *RET* mutations (four MEN 2A in codon 634, two MEN 2B in codon 918, and two others), whereas no significant *RET* mutation was found in seven patients with isolated MTC and no family history or other endocrinopathies.

RET mutations can occur as a germline event (i.e., *RET* mutations occur both in blood and in tumors) in MEN 2A, MEN 2B, and familial MTC. MEN 2B is usually caused by mutations in the tyrosine kinase domain (in 95% of cases involving codon 918, and in 5% codon 883). MEN 2A and familial MTC mutations affect primarily the cysteine-rich domain (codons 609, 611, 618, 620, 630, and 634). In MEN 2A, codon 634 is most frequently affected (85%), whereas in familial MTC the mutations are more evenly distributed among the various codons.[2] In 20-50% of sporadic MTCs, somatic *RET* mutations (i.e., *RET* mutations in tumors but not in blood) have been found.[2]

In a phase I trial of cabozantinib (XL184, a VEGFR, MET, and RET inhibitor), germline and somatic *RET* genotyping for the patients with MTC (n = 37) was performed using DNA isolated from whole blood (n = 30) and tumor (n = 31), respectively. Three MTC patients had germline *RET* mutations, while 23 MTC patients had somatic *RET* mutations.[3]

It is strange that Chang et al in their study found no significant *RET* mutation in seven patients with isolated MTC without a family history and other endocrinopathies. On careful reading of the "Patients and Method" section of their report, I found that only blood or buccal mucosa, not tumors, were genotyped for *RET* mutations. It is possible that seven "isolated" MTC patients had sporadic MTC, not familial MTC; and that some of them had *RET* mutations in their tumors. I think it is important for the authors to comment on this issue and perhaps reply within the context of the Journal.

References

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